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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,334	10/27/2005	Mikhail I Papisov	049479-0041(MGH 2170 US)	1459

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EXAMINER	
CHU, YONG LIANG	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,334	PAPISOV ET AL.	
	Examiner	Art Unit	
	Yong Chu	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,19-22,32-51,54-56,58 and 59* is/are pending in the application.

4a) Of the above claim(s) *32-40,44-51,54-56,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14,19-22, and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Upon entry of the Amendment filed on 11/09/2007, claims 1-12, 14, 19-22, 32-51, 54-56, and 58-59 are pending in the instant application.

Information Disclosure Statement

Applicants' Information Disclosure Statement, filed 01/18/2005, has been considered. Please refer to Applicant's copy of the PTO-1449 submitted herewith.

Priority

This application is a 371 of PCT/US03/22584, filed on 07/18/2003, and claims benefit of U.S. Provisional Patent Application No. 60/397,283, filed on 07/19/2002.

Response to Lack of Unity/Restriction Requirement

Applicants' election without traverse of Group III (claims 1, 13, and 41-43, wherein M as a biologically active modifier), and elected species as **Compound 7** found on page 95 of the specification for initial search purpose has been acknowledged. Since the elected species also reads on the other groups, the Examiner has withdrawn the restriction requirement among product claims 1-12, 14, 19-22, and 41-43. Therefore, the product claims will be examined together, and the method to use claims are non-elected subject matter. Claims 1-12, 14, 19-22, and 41-43 will be examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The said claims are rejected due to claiming a conjugate associate with a diagnostic agent. By definition, a diagnosis In medicine, **diagnosis** or **diagnostics** is the process of identifying a medical condition or disease by its signs, symptoms, and from the results of various diagnostic procedures. The conclusion reached through this process is called *a diagnosis*. The term "diagnostic agent" designates any substance which can be used to serve the purpose. However, the specification lack of description in the way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More specifically, how the claimed conjugate associates with the diagnostic agent is not described and defined.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The term "derivatives" at the last line of each said claims is used to define the claimed conjugate. By definition in chemistry field, a derivative is a compound derived or obtained from another and containing essential elements of the parent substance. However, the specification does not define as the essential elements of the parent substance, and therefore renders the claims indefinite.

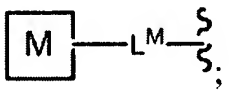
Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5, 7-10, 21, and 41 are rejected under 35 U.S.C. 102 (b) as being anticipated by Cervigni et al., *Angew. Chem. Int. Ed. Engl., (1996), 35(11), pp.1230-1232,* ("Cervigni et al.").

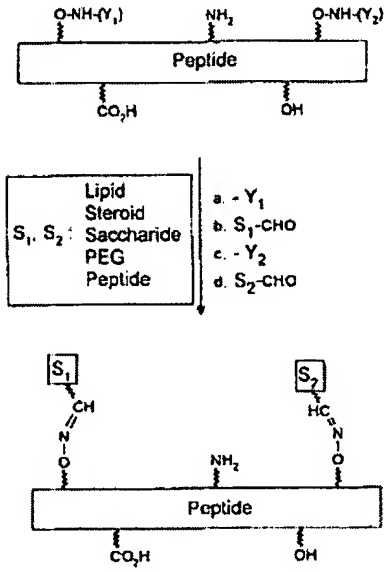
Applicants' instant elected invention of claims 1-2, 5, 7-10, 21, and 41 relates to a conjugate comprising a carrier substituted with one or more occurrence of a moiety having the structure according to claim 1:



> wherein each occurrence of M is independently a biologically active modifier; and each occurrence of L^M is independently an oxime-containing linker.

or a composition comprising the said conjugate.

Cervigni et al. disclosed an oxime-containing conjugate,



Scheme 1. Strategy for regioselective oxime bond formation. a) and c) Selective deprotection of the amino-oxy functions (Y_1, Y_2: orthogonal protecting groups such as *tert*-butyloxycarbonyl (Boc) and allyloxycarbonyl (Alloc); b) and d) Oxime formation in acetate buffer (S_1, S_2: aldehyde-containing compounds). PEG = polyethyleneglycol.

, wherein M is peptide, and the carrier can be either one of S1 and S2, as lipid, saccharide, PEG, peptide, etc., linked by oxime-bonding (-O-N=CH-), and a method to make and use such conjugate. This disclosure anticipates the instant claimed invention. Since the said conjugate is claimed for biological application, the composition comprising said conjugate thereof is also anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

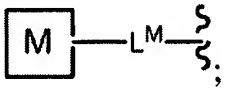
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 14, 19-22, and 41-43 are rejected under 35 U.S.C. 103 (a) as unpatentable over Cervigni et al., in view of *U.S. Patent No. 5,958,398* by Papisov ("the `398 patent"), *U.S. Patent No. 5,612,037* by Huebner ("the `037 patent"), and G. Hermanson, Preparation of Liposome Conjugates and Derivatives, Bioconjugate Techniques, pp. 552-569, ("Hermanson").

Applicants' instant elected invention of claims 1-12, 14, 19-22, and 41-43 relates to a conjugate comprising a carrier substituted with one or more occurrence of a moiety having the structure according to claim 1:

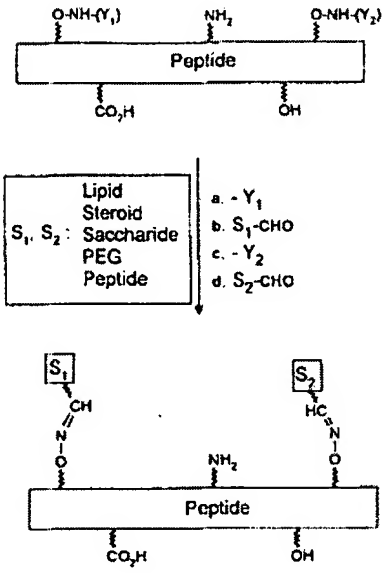


wherein each occurrence of M is independently a biologically active modifier; and each occurrence of L^M is independently an oxime-containing linker.

or a composition comprising the said conjugate, wherein M is a biologically active modifier, and the carriers are biodegradable polymer, liposome,etc.

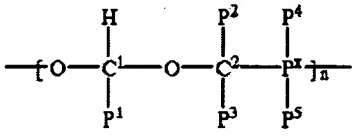
Determination of the scope and content of the prior art (MPEP §2141.01)

Cervigni et al. disclosed an oxime-containing conjugate,



Scheme 1. Strategy for regioselective oxime bond formation. a) and c) Selective deprotection of the amino-oxy functions (Y_1, Y_2: orthogonal protecting groups such as *tert*-butyloxycarbonyl (Boc) and allyloxycarbonyl (Alloc); b) and d) Oxime formation in acetate buffer (S_1, S_2: aldehyde-containing compounds). PEG = polyethyleneglycol.

, wherein M is peptide, and the carrier can be either one of S1 and S2, as lipid, saccharide, PEG, peptide, etc., linked by oxime-bonding (-O-N=CH-), and a method to make and use such conjugate.

The `398 patent disclosed a biodegradable polyacetyl polymer having a specific unit structure  . This crosslinked diodegraddable biocompatable polyacetyl gel can further reacted with a drug to form a conjugate, as disclose on lines 51-52, column 7 of the `398 patent.

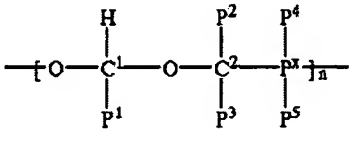
The `037 patent disclosed a conjugate of influenza virus hemagglutinin (HA) to carrier protein with bifunctional esters such as MCS, MBS, SMCC, SMPP at lines 7-67, column 3, as a influenza vaccine.

Hermanson taught methods of coupling a biological active molecule such as antibody, protein, or biotinylated compound to a liposome carrier for biological applications, also see the incorporated references by Hermanson.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the Cervigni prior art and the instantly claimed invention is that Cervigni et al. teach a oxime conjugate of a carrier and modifier, but do not teach all the specific carrier such as polyketal as in claims 12 and 14; maleiimide- or N-hydroxysuccinimide ester containing crosslinker as in claims 3 and 4; or a liposome based carrier.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

However, to one ordinary skilled in biochemistry and medicinal chemistry arts such differences in claimed limitations would be *prima facie* obvious over the combined prior art teachings. It is because using the polyketal as a carrier of the conjugate in claims 12 and 14 has been taught in the `398 patent as a biodegradable polyacetyl polymer having a specific unit structure  , and suggested to crosslink with a drug to form a conjugate. The biological conjugate of a biological modifier such as immunogenic protein and a carrier such as carrier protein for biological application such as vaccine has been taught and/or suggested by the `037 patent. Finally, the lipid/liposome carriers are taught and or suggested by Hermanson for biological applications, also see the incorporated references by Hermanson. Therefore, the instantly claimed invention is obviousness.

Double Patenting

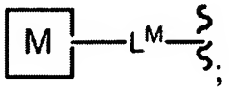
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12, 14, 19-22, and 41-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-42 of copending Application No. 10/501,565 ("the `565 application") in view of Cervigni et al., *U.S. Patent No. 5,612,037* by Huebner ("the `037 patent"), and G. Hermanson, Preparation of Liposome Conjugates and Derivatives, Bioconjugate Techniques, pp. 552-569, ("Hermanson"). Although the conflicting claims are not identical, they are not patentably distinct from each other because they teach the same claimed sub-genus.

Applicants' instant elected invention of claims 1-12, 14, 19-22, and 41-43 relates to a conjugate comprising a carrier substituted with one or more occurrence of a moiety having the structure according to claim 1:

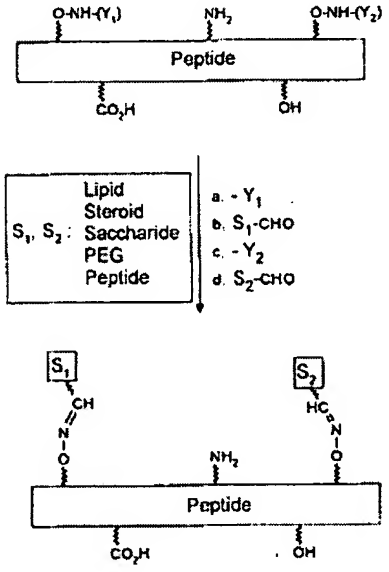


wherein each occurrence of M is independently a biologically active modifier; and each occurrence of L^M is independently an oxime-containing linker.

or a composition comprising the said conjugate, wherein M is a biologically active modifier, and the carriers are biodegradable polymer, liposome,etc.

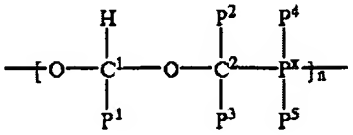
Determination of the scope and content of the prior art (MPEP §2141.01)

Cervigni et al. disclosed an oxime-containing conjugate,



Scheme 1. Strategy for regioselective oxime bond formation. a) and c) Selective deprotection of the amino-oxy functions (Y_1, Y_2: orthogonal protecting groups such as *tert*-butyloxycarbonyl (Boc) and allyloxycarbonyl (Alloc); b) and d) Oxime formation in acetate buffer (S_1, S_2: aldehyde-containing compounds). PEG = polyethyleneglycol.

, wherein M is peptide, and the carrier can be either one of S1 and S2, as lipid, saccharide, PEG, peptide, etc., linked by oxime-bonding (-O-N=CH-), and a method to make and use such conjugate.

The `565 application claims a biodegradable biocompatible polyketal polymer having a specific unit structure  with a nitrogen-containing moiety, wherein the said moiety is a pharmaceutical useful group, a drug, a macromolecule, or a diagnostic label.

The `037 patent disclosed a conjugate of influenza virus hemagglutinin (HA) to carrier protein with bifunctional esters such as MCS, MBS, SMCC, SMPP at lines 7-67, column 3, as a influenza vaccine.

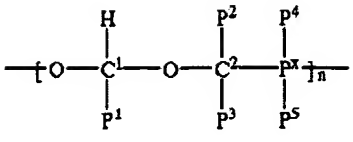
Hermanson taught methods of coupling a biological active molecule such as antibody, protein, or biotinylated compound to a liposome carrier for biological applications, also see the incorporated references by Hermanson.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the Cervigni prior art and the instantly claimed invention is that Cervigni et al. teach a oxime conjugate of a carrier and modifier, but do not teach all the specific carrier such as polyketal as in claims 12 and 14; maleiimide- or N-hydroxysuccinimide ester containing crosslinker as in claims 3 and 4; or a liposome based carrier.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

However, to one ordinary skilled in biochemistry and medicinal chemistry arts such differences in claimed limitations would be *prima facie* obvious over the combined prior art teachings. It is because using the polyketal as a carrier of the conjugate in claims 12 and 14 has been claimed in the `565 application as a biodegradable polyacetyl polymer

having a specific unit structure  , and suggested to crosslink with a drug to form a conjugate. The biological conjugate of a biological modifier such as immunogenic protein and a carrier such as carrier protein for biological application such as vaccine has been taught and/or suggested by the `037 patent. Finally, the lipid/liposome carriers are taught and or suggested by Hermanson for biological applications, also see the incorporated references by Hermanson. Therefore, the instantly claimed invention is obviousness.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

- Claims 1-12, 14, 19-22, and 41-43 are rejected.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Chu whose telephone number is 571-272-5759. The examiner can normally be reached between 7:00 am - 3:30 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571-272-0699. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

REBECCA ANDERSON
PRIMARY EXAMINER

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Patent Examiner
Art Unit 1626

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